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Original Research Paper

The effects of *Sambucus nigra* berry on acute respiratory viral infections: A rapid review of clinical studies

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ABSTRACT

Brief overview: Collectively the evidence obtained from across five clinical studies involving 936 adults indicate that mono-herbal preparations of *Sambucus nigra* L. berry (*S.nigra*), when taken within 48 hours of the onset of acute respiratory viral infection, may reduce the duration and severity of common cold and influenza symptoms in adults. There is currently no evidence to support the use of *S.nigra* berry for the treatment or prevention of COVID-19. Given the body of evidence from preclinical studies demonstrating the antiviral effects of *S.nigra* berry, alongside the results from clinical studies involving influenza viral infections included in this review, pre-clinical research exploring the potential effects of *S.nigra* berry on COVID-19 are encouraged.

Verdict: The evidence included in this review is mostly derived from clinical studies involving adult participants and examining short-term use of commercial formulations of *S.nigra* berry for up to 16 days. Findings from included studies suggest that mono-herbal preparations of *S.nigra* berry (in extract or lozenge formulation) may reduce influenza-type symptoms, including fever, headache, nasal congestion and nasal mucous discharge in adults, when taken within the first 48 hours of symptom onset. Within 2–4 days of *S.nigra* treatment, most adult participants experienced significant symptom reduction, by an average of 50%. Evidence regarding the effectiveness of *S.nigra* berry on the symptom of cough, and need for/use of medicines (including antibiotics) to treat acute respiratory infections, is currently unclear and inconsistent. Adverse events were rare with no serious events reported. Adverse events, reported in two studies, were more common in comparators than in treatments. There is currently no reliable or sufficient scientific evidence to support the use of *S.nigra* in pregnant or lactating women.

1. Background

The *S. nigra* plant belongs to the Adoxaceae family, which is indigenous to Europe, Asia and North Africa [1]. Historically, the flower and berry of the Elder plant have been used in herbal preparations for the treatment of common cold and flu [1]. Preclinical studies have shown elderberry extracts to have antimicrobial and antiviral effects, including activity against influenza viruses [2]. These antiviral effects have been attributed to the inhibition of viral replication by *S.nigra*. Additionally, elderberry extracts have been shown to increase cytokines that activate immunomodulation [3].

S.nigra berries contain multiple constituents, including flavonoids, triterpenes, acyl spermidines, α-linolenic acid, linoleic acid [1], mucilage and hydroxycinnamic acid derivatives [4]. The rich anthocyanin flavonoid content is associated with antioxidant activity [5]. The unripe berries also contain toxic constituents, but

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these are lost during drying and heating processes; as such, these toxic constituents are not typically present in commercially available preparations [3].

2. Search strategy

2.1. Research question

Does *S.nigra improve* outcomes in humans with acute respiratory viral infections?

2.2. Inclusion/exclusion criteria

2.2.1. Inclusion criteria

Original prospective intervention studies involving adult participants with acute respiratory viral infections written in English that evaluated the effect of *S.nigra* (as a mono- or combination therapy) in any form, dose and route of administration. All comparators or controls were included.

2.2.2. Exclusion criteria

Studies soley involving children, or participants with bacterial, fungal or non-infectious respiratory disease and not meeting the inclusion criteria above were excluded from this review.

2.3. Databases

Relevant studies were identified by searching MEDLINE (Ovid), EMBASE (Ovid), AMED (Ovid) and CINAHL (EBSCO) for articles published from inception to May 2020.

2.4. Search terms

Example – MEDLINE (Ovid):

(((Randomized Controlled Trials as Topic/ OR randomized controlled trial/ OR Random Allocation/ OR Double Blind Method/ OR Single Blind Method/ OR clinical trial/ OR clinical trial, phase i.pt. OR clinical trial, phase ii.pt. OR clinical trial, phase iii.pt. OR clinical trial, phase iv.pt. OR controlled clinical trial.pt. OR randomized controlled trial.pt. OR multicenter study.pt. OR clinical trial.pt OR exp Clinical Trials as topic/) OR ((clinical adj trial$).tw. OR ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. OR PLACEBOS/ OR placebo$.tw. OR randomly allocated.tw. OR (allocated adj2 random$).tw.)) NOT (case report.tw. OR letter/ OR historical article/)) AND (“Sambucus niger” OR “Sambucus nigra” OR Sambuc* OR Elderberry.af.) AND ((Influenza, Human/ OR Influenza A Virus, H1N1 Subtype/ OR Influenza A virus/ OR Influenza A Virus, H3N2 Subtype/ OR H1N1.mp.) OR (MERS−COV.mp. OR Middle East Respiratory Syndrome Coronavirus OR SARS OR severe acute respiratory syndrome/) OR ((breathing or lung or pulmonary or respir$).af.))

2.5. Screening and data extraction

One author (KO) scanned the title and abstract of each record retrieved. All articles that appeared to meet the selection criteria were accessed and evaluated in full text. For articles that met the inclusion criteria, two authors (KO and JMC) extracted the relevant population and intervention characteristics into an extraction template, with any disagreements resolved by discussion with AS. Where duplicate papers and papers reporting aspects of the primary study, the authors (JMC and AS) checked the data aligned before removing the secondary paper and the original publication (typically the older paper) was included.

The risk of bias of each study was evaluated by KO and JMC, using the Cochrane Collaboration Risk of Bias tool [6], and checked by AS. Any disagreements were resolved by consensus. The Cochrane Risk of Bias tool is comprised of seven domains including; random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Reviewers designated a judgement related to the risk of bias for each item. 'Yes' indicated a low risk of bias, and 'No' a high risk of bias and 'Unclear' indicating unclear or unknown risk of bias.

2.6. Data analysis

Data were synthesised in narrative form. Due to the heterogeneity of the data, a meta-analysis was not conducted.

3. Rapid review results

The database search identified 40 studies. After the removal of duplicates (n = 10), 30 studies were screened by title and abstract. This resulted in the exclusion of 15 studies. The remaining 15 studies were screened as full text. Ten studies were excluded as they reported the wrong study design (n = 4), were a systematic review (n = 4) or duplicated already included studies (n = 2). Five studies were included for full review. (see Table 1)

Included studies were conducted in China [n = 1], Australia [n = 1], Israel [n = 1], Czech Republic [n = 1] and Norway [n = 1]. All studies were randomized, double-blind controlled trials. Four studies used a placebo control, and one study [7] used an active control (i.e. oseltamivir). The duration of included studies ranged from 2 to 16 days.

The included studies involved a total of 936 participants (minimum 27, maximum 473, mean 187). The study population were primarily adults aged between 18 and 70 years, with two studies also including children aged from 5 years [7] or 12 years [8]. The most common conditions studied were influenza [7–9] and influenza-like symptoms [10], followed by common cold [11].

All included studies used a proprietary herbal medicine product as the intervention. Four studies used mono-herbal preparations of *S.nigra* berry extract [7,9–11]. One study used a poly-herbal preparation, which contained *S.nigra* berry plus *Echinacea purpurea* root [8]. The preparations were administered orally in the form of a syrup [7,10], capsules [11], granules [8] or lozenges [9]. Doses ranged from 15 mLs four times per day (syrup), 3 capsules per day, 175 mg lozenge four times per day or 5 mL of the poly-herbal formula in 150 mL of hot water using an initial dosage of 5 times per day for days 1−3 followed by a maintenance dose of twice per day (days 4−10).

3.1. Critical appraisal

As presented in Table 2, the risk of bias assessment for the first domain (randomisation process) resulted in all 5 studies being rated as having a low risk of bias [7–11]. For domain 2 (treatment assignment), two studies were considered to have some concerns [8,9], and three studies were rated as having low risk of bias [7,10,11]. Under domain 3 (missing outcome data), all five trials were judged as having low risk of bias [7–11]. For domain 4 (measure of outcomes), all five studies were rated as having low risk of bias [7–11]. In domain 5 (selective reporting), all trials were judged to be at low risk of bias [7–11]. Overall, two studies were identified as having some concerns [8,9] and three studies were judged as having low risk of bias [7,10,11]. These judgements should be taken into consideration when interpreting the findings of this review.

Table 1
Summary of Included Studies.

Identification		Methods			Intervention							Outcomes	
Author (date)	Country	Design	Study duration	Statistical method (s)	Study Population (age)	Disease or Condition	Intervention (single or mixed formula)	Administration	*Dose*	Duration of Treatment	Control or Placebo	Measure of Outcome	Outcome
Zakay-Rones, Z et al (1995)	Israel	*In-vitro* plus double-blind clinical trial -	3 days plus 6 days follow-up	Fisher exact test; odds ratio summary measure	n = 27; 5–56 years;	Influenza A; Influenza B; RSV; adeno-RSV; clinical trial during Influenza B/ Panama	Single formula - Sambucol - standardized extract of Sambucus nigra berries	oral (syrup)	children = 2 tablespoons daily; adults = 4 tablespoons daily	3 days	placebo	Symptom reduction - fever improvement	Treatment: mean = 2.36 ± 0.9 day Control: 3.33 ± 1.5 days
												Symptom improvement - day 1	Treatment: 20%, Control: 8.3%
												Symptom improvement - day 2	Treatment: 73.3% Control: 16.7%
												Symptom improvement - day 3	Treatment: 6.7% Control = 33.3%
												Duration of illness (no. of days)	Treatment: 2.7 days Control: 4 days
Zakay-Rones, Z et al (2004)	Israel, Norway, Sweden	Randomized, double-blind, placebo-controlled; multi-centre (n = 4)	5 days plus 5 days follow-up	Continuous variables - mean values student's t; two-tailed tests; analysis of variance with repeated measures; analysis	n = 60; 18–54 years	influenza-like symptoms	Standardised extract of Sambucus nigra berries (Sambucol) - 38% in a syrup also containing raspberry extract, glucose, citric acid and honey.	oral (syrup)	15 ml - 4 per day	5 days	Placebo (Conventional concomitant medications permitted including analgesic and/or metered dosage nasal spray)	Symptom observation via visual analogue scale - at baseline, 4 times per day + twice daily for five days post treatment.	*Symptom reduction* – Treatment: 3–4 days Control: 7–8 days Full recovery by all by day 8;
												Measures = no improvement - pronounced; improvement on 10 point scale;	*Pronounced improvement* – Treatment: mean 3.1 days (SD 3.1) Control: 7.1 days (SD 2.5) (p<0.001)
												Use of 'rescue' medication	Less use of 'rescue' medication by treatment group (p <0.001)
Tiralongo, E et al (2016)	Australia	Randomized, double-blind placebo-controlled clinical trial	April 2013 - December 2014	Chi Square or Fischer's exact test; ANOVA group comparison	N = 312 Mean: 51y (SD 16)	Common cold	Standardised extract, membrane filtered, 300 mg of elderberry extract (22% polyphenols 15% anthocyanins and 150 mg of rice flour. The 300 mg elderberry extract also contain several mineral, trace elements and vitamins including relatively high levels of magnesium 1.19 mg (3.97 mg/g).	oral (capsules)	Priming dose = 2 capsules per day; Overseas dose = 3 capsules per day	Between 15 and 16 days - variable by travel duration per participant	placebo	Cold episodes (total number of days measured for previous 6 days)	No difference between groups
												Cold duration (no. days)	Treatment: 57 days Control: 117 days (p = 0.05)
												Cold symptoms (score)	Treatment: 247 Control: 583 (p = 0.02)
												Co-medication (eg nasal spray, cold tablets, analgesic, antibiotic)	No difference between groups.

Kong, F (2009)	China	Pilot, randomized, double-blind, placebo-controlled clinical trial	2 days	Two-tailed tests	N = 64 16–60 years	influenza	175 mg of the proprietary elderberry extract plus non-active ingredients (maltodextrin, dextrose, fructose, silica, citric acid, natural flavors, cyclodextrin and magnesium stearate).	Slow-dissolve lozenge	175mg - 4 per day	2 days	placebo	Total symptom severity – 48 hours (VAS score)	Treatment: no symptoms (n=9; 28%), some symptom relief (one or two mild symptoms; VAS=1) (n=19; 60%), mean VAS score 0.28 (SD 0.63). Control: No participants had symptom resolution or relief.
												Fever – 48 hours (VAS score)	Treatment: Decreased from baseline (2.67, SD 1.80) to 0.47 ± 0.64 (p<0.0001).
												Headaches – 48 hours (VAS score)	Treatment: Decreased from baseline 4.47 (SD 2.14) to 1.53 (SD 1.41) (p<0.0001) Control: increased from 3.78 (SD 1.66) to 5.25 (SD 1.34) (p <0.0001)
												Muscle aches – 24 hours, 48 hours (VAS score)	*24 hours* Treatment: Decreased from baseline (2.87, SD 2.13) to 1.19 (SD 1.05) (p=0.0002) *48 hours* Treatment: 0.16 (SD 0.45) by 48 hours. Control: Increased from baseline 2.13 (SD 2.10) to 3.47 (SD 1.50) (p=0.0013)
												Nasal congestion – 24 hours, 48 hours (VAS score)	*24 hours* Treatment: Decreased from baseline 4.03 (SD 2.10) to 1.47 (SD 1.14 (p<0.0001) *48 hours* Treatment: 0.56 (SD 0.62) Control: increased from baseline 3.30 (SD 1.71) to 4.26 (SD 1.81) (p=0.049).
												Nasal mucus discharge - 48 hours (VAS score)	Treatment: Decreased from baseline 1.94 (SD 1.61) to 0.50 ± 0.52 (p = 0.0019) Control: No significant improvement.

Table 1 (*Continued*)

Identification		Methods			Intervention							Outcomes	
Author (date)	Country	Design	Study duration	Statistical method (s)	Study Population (age)	Disease or Condition	Intervention (single or mixed formula)	Administration	*Dose*	Duration of Treatment	Control or Placebo	Measure of Outcome	Outcome
												Coughing - 48 hours (VAS score)	Treatment: No significant change from baseline Control: increased from baseline 2.19 (SD 1.47) to 3.69 (SD 1.25) (p = 0.0041).
Raus et al. (2015)	Czech Republic	DBRCT double dummy, multicentre	10 days	Wilcoxon test	N = 473 12–70 years (<18 years, n = 9)	Active influenza symptoms	Hydroethanolic extract (65% v/v) of freshly harvested *Echinacea purpurea*. extraction ratio 1:12 of herb and 1:11 from the roots combined at a ratio of 95% to 5%. 240mg of the active ingredient concentrated to extractum spissum, supplemented with 276.5 mg Sambucus fructus succus recentis and excipients to give 1 mL Echinaforce Hotdrink	Experimental group: 5 mL Echinaforce Hotdrink in 150 mL hot water and 3 × 5 mL in 150 mL hot water and placebo oseltamivir Placebo group: Echinaforce hot drink placebo (same dose as above) and Oseltamivir verum Oseltamivir placebo	5 times/day BD BD 5 times/day BD BD BD	Days 1–3 Days 4–10 Days 1–10 Days 1–3 Days 4–10 Days 1–5 Days 6–10	Echinaforce Hotdrink placebo contained the same excipients as the verum plus colorants and flavors. Oseltamivir placebo was manufactured by overen. Capsulation of original oseltamivir capsules using opitically dense dark green gelatin capsules filled with microcrystalline cellulose	Cumulative proportion of patient with influenza symptoms alleviated (Day 1) Cumulative proportion of patient with influenza symptoms alleviated (Day 5) Cumulative proportion of patient with influenza symptoms alleviated (Day 10) Non-inferiority of treatment vs control (generalized Wilcoxon test) Incidence of recovery (the first day when cough, nasal obstruction, sore throat, fatigue, headache, myalgia, and feverishness were rated as absent or mild in the evening). Adverse events	Treatment: 1.5% Control: 4.1% Treatment: 50.2% Control: 48.8% Treatment: 90.1% Control: 84.8% P[x<Y] = 0.5068; 95% CI, 0.4871–0.5265. No difference found in subgroup of virologically confirmed influenza, and in retrospective analysis during the peak influenza period. Recovery rates were similar between the two groups. Treatment: 2.46% Control: 6.45%; (P = 0.076)

Table 2
Critical appraisal of Included Studies.

Author (date)	Randomisation process	Treatment assignment	Missing outcome data	Measure of outcomes	Selective reporting	Overall risk of bias
Zakay-Rones, Z et al. (1995)	Low	Low	Low	Low	Low	Low
Zakay-Rones, Z. et al (2004)	Low	Low	Low	Low	Low	Low
Tiralongo, E. et al (2016)	Low	Low	Low	Low	Low	Low
Kong, F (2009)	Low	Low	Some concerns	Low	Low	Some concerns
Raus, K. et al. (2015	Low	Low	Some concerns	Low	Low	Some concerns

3.2. Summary of findings

Treatment outcomes reported included overall reduction in symptoms; duration of illness/rate of recovery, and the use of rescue medication including analgesics, nasal spray, cold tablets, antibiotics.

Four studies [7,9–11] measured reduction of symptoms; fever reduction [7,9–11] and one study [9] also reported reduction of headache, muscle ache, nasal congestion and mucus discharge and cough All studies reported [7,10,11] a reduction in overall symptom severity among participants receiving *S.nigra* berry (whether in mono- or poly-herbal formulation) when compared with controls. One study reported that participants receiving treatment reported significant improvement in symptom severity following 48 h whereas the control group reported increased severity in the same time-period [8]. Duration of illness and rate of recovery was reported in four studies [7,8,10,11]. Three studies demonstrated that the duration of illness was almost 50 % shorter for those receiving *S.nigra* berry compared with the control group [7,10,11]. In one study, the rate of recovery was similar between a *S.nigra* polyherbal preparation and an active control (Oseltamivir) [8].

In the two studies [10,11] reporting the use of rescue medication including analgesics, antibiotics, nasal sprays, or cold tablets to manage participant symptoms, the need for such medication was found to be inconsistent. In one study, participants assigned to *S.nigra* berry treatment reported using rescue medication to manage influenza-like symptoms less frequently than control participants [10]. By contrast, a second study found no difference between groups in the reported use of rescue medication or prescribed antibiotics among participants with the common cold [11].

3.3. Adverse events

Adverse events were rare with one study [11] reporting two adverse events (fatigue and cold-like symptoms) attributed to *S. nigra* berry compared to three (itchy throat, fatigue and kidney pain) attributed to placebo. A second study [8] reported nine adverse events (nausea and vomiting) attributed to treatment (a poly-herbal formulation containing *S.nigra* berry and *Echinacea purpurea* extract) compared with 18 reported adverse effects attributed to the comparator (Oseltamivir). No serious adverse events were reported.

3.4. Clinical significance

Overall, the evidence obtained from the five studies included in this review involving 936 people suggests that mono-herbal preparations of *S.nigra* berry when taken close to the onset of symptoms and for up to two weeks, may assist in relieving the symptoms of the common cold and influenza. *S.nigra* berry may be effective in reducing the duration and severity of fever, headache, nasal congestion and nasal mucous discharge when associated with an acute viral respiratory infection. Some evidence suggests that *S.nigra* berry may relieve cough or help prevent the worsening of cough when attributed to such viral infections however this finding is inconsistent across studies. As the formulation, dose and duration of *S.nigra* berry treatment varied between studies, general recommendations regarding these clinically important factors cannot be made. Accordingly, TGA-approved monographs and pharmacopoeias [12] and the studies included in this review should be consulted when making decisions regarding dosing of *S. nigra* berry treatment. It is important to note that none of the studies included evaluation of the use of *S.nigra* berry in pregnant and/or breastfeeding women or in people with chronic or complex conditions. No studies investigated the use of *S. nigra* berry in the treatment, prevention, or relief of symptoms of COVID-19. While there is some evidence to suggest *S.nigra* berry increases inflammatory cytokines IL-1 beta, TNF-alpha, IL-6, IL-8 [13], there is no strong evidence to date to support that *S.nigra* berry can contribute to a cytokine storm. Both efficacy and safety studies are warranted to answer these important clinical questions.

Disclaimer

This article should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

Authors' contributions

DA and AS refined the research question and developed the search strategies. DA undertook the searches. KO screened the English-language citations by title, abstract and full text. DB searched and attached full text. KO and JMC extracted data from the included papers. KO and JMC performed the Risk of Bias assessments using the revised Cochrane Risk of Bias tool for randomized trials (RoB2).

JMC drafted the Risk of Bias summary. AS drafted the results. TAP drafted the clinical significance summary. JH, DA, and AS drafted the background, search strategy and methods sections of the manuscript. JH drafted the overview and verdict sections. ML and JH critically revised the Rapid Review.

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